



NOTES

OPPORTUNISTIC FUNGAL INFECTIONS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Range of infections caused by fungi; take advantage of weakened immunity (e.g. HIV/AIDS, malignancy, immunosuppression), altered microbiota, breached integumentary barriers
- Present in environment worldwide → immunocompetent, healthy individuals can be exposed without resulting in disease

RISK FACTORS

- Immunosuppression (e.g. HIV/AIDS, neutropenia, chemotherapy, hematologic malignancies, transplant recipients)

SIGNS & SYMPTOMS

- Primary local cutaneous, pulmonary infection to dissemination to various internal organs

DIAGNOSIS

LAB RESULTS

- Direct microscopy with staining, culture, tissue biopsy, bronchoalveolar lavage (sputum sample if pulmonary in origin), polymerase chain reaction (PCR)

TREATMENT

MEDICATIONS

- Antifungals

ASPERGILLUS FUMIGATUS

osms.it/aspergillus-fumigatus

PATHOLOGY & CAUSES

- Saprophytic fungi species responsible for majority of invasive, chronic aspergillosis
- Found in soil, compost
- Asexual reproduction → production of green pigmented asexual conidia (spores) → aerosolized → individuals inhale everyday → macrophages attempt to clear conidia → secondary inflammation after conidia germinate into hyphal forms → neutrophil recruitment → activation of

cellular immunity to kill hyphae

- Histopathologically, **invasive aspergillosis** characterized by progression across tissue planes
 - **Hallmark:** vascular invasion → infarction + tissue necrosis
- Characteristics of *Aspergillus* as successful opportunistic pathogen
 - Ability to grow at 37°C/98.6°F
 - Small conidial (2.5–3 micrometers) → buoyant in air for prolonged periods of time → inhaled deeply into lung alveoli

VISIT...

LANZAROTE
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- *Aspergillus* hyphae angioinvasive
 - Thrombose arteries → hemorrhagic infarcts → abscesses
- Suspect in immunocompromised individuals with respiratory distress, fever (despite broad-spectrum antibiotics)
- Second most common cause of invasive fungal infections in neutropenic individuals (after *Candida* species)
- Specifically affects pulmonary, sinus, central nervous system (CNS)

Diseases

- Necrotizing otitis externa
 - More common in advanced HIV cases
- Acute pulmonary aspergillosis
 - Inhaled conidia
 - Most common cause of death in persons with chronic granulomatous disease (CGD)
 - Can spread locally to involve pleura, chest wall, vertebrae → dissemination to other organs

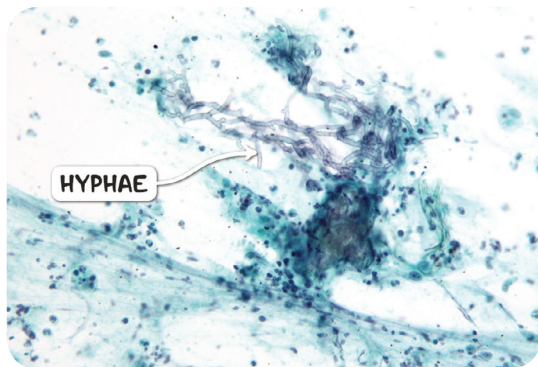


Figure 84.1 Bronchial washing stained with Grocott methenamine silver stain from an individual with pulmonary aspergillosis. The hyphae are uniform, narrow and branch at acute angles.

- Cerebral aspergillosis
 - Occurs in approx. 40% of individuals with invasive aspergillosis
 - Hematogenous dissemination from extracranial focus (e.g. lung)/direct extension from sinus
 - Most common brain abscess in stem cell transplant individuals

- Pulmonary aspergilloma
 - Nonsaprophytic (noninvasive)
 - Colonization of pre-existing cavities (e.g. tuberculosis, sarcoidosis, bullous emphysema, bronchiectasis)
 - Occurs in 15–25% of persons with cavitating lung disease from tuberculosis
 - Lesion impinges on major vessel/airway → massive hemorrhage → hemoptysis
 - “Fungus ball”
- Allergic bronchopulmonary aspergillosis
 - Exposure to allergens of *A. fumigatus* → saprophytic growth → colonization of bronchial lumen → persistent bronchial inflammation → IgE-mediated allergic response in airways → hypersensitivity lung disease → bronchial obstruction
 - Affects those with asthma (1–2%)/cystic fibrosis (1–15%)

RISK FACTORS

- Decreased immunity
 - Malignancy, chemotherapy, transplant (esp. from HLA-mismatched donor), HIV/AIDS, immunosuppressant therapy, neutropenia, prolonged high dose corticosteroid use
- Prior pulmonary damage/disease
- ↑ age
- History of tuberculosis, histoplasmosis, sarcoidosis, bronchiectasis
- Cystic fibrosis, asthma (allergic bronchopulmonary aspergillosis)

COMPLICATIONS

- Hemorrhage → massive hemoptysis
- Widespread bronchiectasis + fibrosis → respiratory failure, death

SIGNS & SYMPTOMS

- Acute pulmonary aspergillosis
 - Unrelenting fever in high-risk cases (most common), dry cough, chest pain, dyspnea (more common in persons with diffuse disease), ↑ erythrocyte sedimentation rate (ESR)

- Invasive sinusitis
 - Ear/facial pain, discharge, swelling; nasal septum/turbinate pallor; epistaxis; orbital swelling, headache; localized areas of frank crusting, ulceration, blackened necrotic areas
- Cerebral infection
 - Headache, nausea, vomiting; altered mental status, confusion, cranial nerve palsies, hemiparesis
- Pulmonary aspergilloma
 - May be asymptomatic; persistent, productive chronic cough, **hemoptysis**, weight loss
- Allergic bronchopulmonary aspergillosis
 - Manifestations due to immune system response to *A. fumigatus* antigens; asthma-like symptoms (e.g. wheezing), eosinophilia
- Invasive aspergillosis
 - Acute onset of fever, cough, respiratory distress, diffuse bilateral pulmonary infiltrates

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- Increased sensitivity for radiological diagnosis
- Halo sign
 - Neutropenic individuals (hemorrhagic nodule due to angioinvasion); rim of ground glass opacity surrounding nodule
- Air crescent sign
 - Can develop from halo sign; **cavitation** → sloughed lung tissue encircled with rim of air

MRI

- Target sign
 - Nodule with lower central signal, higher contrast-enhancing signal on periphery; late stage disease
- For diagnosis of cerebral aspergillosis; multiple lesions in basal ganglia

X-ray

- Unilateral **infiltrates** (interstitial, alveolar, mixed), cavitary lesions, multiple nondefined 1–3cm. 0.39–1.18in peripheral nodules coalesce into larger masses

LAB RESULTS

Tissue biopsy

- Not utilized frequently due to invasive nature; ↑ risk of bleeding or secondary infection in immunosuppressed individuals

Cultures

- Respiratory tract, sputum cultures commonly negative; rarely diagnosed by blood

Bronchoalveolar lavage

- Approx. 40% diagnostic yield

Serology

- Useful for diagnosis of aspergilloma, allergic bronchopulmonary aspergillosis in immunocompetent individual; not useful in immunocompromised

Galactomannan antigen testing

- Enzyme immunosorbent assay recognizes side chains of galactomannan molecule
 - **Positive:** invasive disease
 - High false-positive rate in neutropenic cases

Allergic bronchopulmonary aspergillosis

- Eosinophilia, ↑ serum IgE

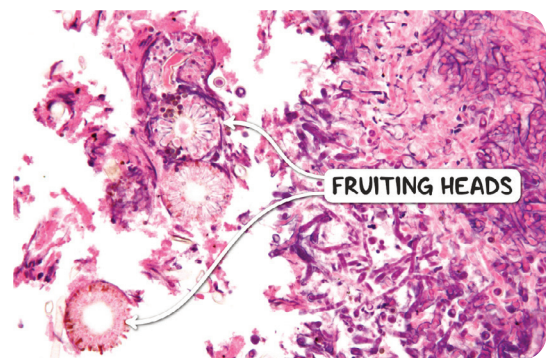


Figure 84.2 A tissue section containing *Aspergillus* hyphae and fruiting heads.

TREATMENT

MEDICATIONS

- Invasive aspergillosis
 - Voriconazole (preferred over amphotericin B)/caspofungin; azole-resistance developing
- Local pulmonary aspergilloma
 - Percutaneous intracavitary instillation of antifungals
- Allergic bronchopulmonary aspergillosis
 - Corticosteroids (attenuate immune system response)
 - **Antifungal therapy:** itraconazole (decrease fungal burden, antigen load)
 - Preventative long term antifungal therapy in immunocompromised individuals

SURGERY

- Local pulmonary aspergilloma
 - Surgical removal (e.g. lobectomy in massive hemoptysis)

CANDIDA

osms.it/candida

PATHOLOGY & CAUSES

- Oval, budding yeast; forms hyphae, pseudohyphae
- Nonpathological colonization of humans → overgrowth leads to pathology
- Most common cause of invasive fungal infections in immunocompromised individuals (e.g. neutropenic cases)
 - *C. albicans* species most common cause of candidiasis
 - Increasing proportion of fungal infections caused by nonalbicans *Candida* species (e.g. *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. glabrata*)

Chronic mucocutaneous candidiasis

- Persistent infection of mucous membranes, skin, nails
- More commonly affects those with defective T-cell mediated immunity

Vulvovaginal candidiasis (VVC)

- Originates from spread from GI tract, sexual transmission
- Occurs in 75% of healthy individuals who are biologically female
 - 80–90% caused by *C. albicans*

- 10–20% of those with VVC have severe, recurrent infections; usually from nonalbicans species

Candida esophagitis

- Most common in severely immunocompromised individuals (e.g. HIV individuals)
- May occur in absence of thrush
- In individuals with AIDS, can occur simultaneously with cytomegalovirus, herpes simplex infection (HSV)

Disseminated/invasive candidiasis

- Rare in immunocompetent individuals
- Development of invasive disease due to interaction between *Candida* species virulence factors, colonization burden, host immunological status
- Candidemia
 - Isolation of *Candida* from blood culture
- *Candida* species exhibit tissue tropism → deep organ involvement (e.g. liver, spleen, brain, bone) in absence of prolonged candidemia

RISK FACTORS

- Antibiotic therapy, diabetes mellitus (poorly controlled), **immunocompromised** state (e.g. immunosuppressive therapy, neutropenia, hematologic malignancy, chemotherapy, transplant), chronic granulomatous disease, Job syndrome, impaired cell-mediated immunity, pregnancy, contraceptive use (hormonal/intravaginal, intrauterine devices)

COMPLICATIONS

- Meningoencephalitis
 - Obstructive hydrocephalus, calcifications, thrombosis
- Renal system
 - Pyelonephritis
- Abscesses in multiple organs
- Sepsis, septic shock

SIGNS & SYMPTOMS

Mucocutaneous growth (most common)

- Mouth, oropharynx
 - AKA **thrush**
 - Thick, pearly **white**, curd-like **plaques** on oral mucosa
 - Painful → dysphagia/odynophagia
 - Otherwise unexplained → suspect HIV infection
- Vagina
 - Thick, cottage-cheese-like, **white** vaginal **discharge**
 - Painless, pruritic
 - Dysuria possible
- Cutaneous candidiasis
 - Erythematous pruritic patches + satellite lesions
 - Individuals who are obese, diabetic
 - Skin folds, underneath breasts
- GI tract
 - May be asymptomatic
 - Esophagus → odynophagia

Disseminated/invasive candidiasis

- **Candidemia**: nonspecific (hard to distinguish from bacteremia); most commonly manifests as persistent fever despite antibiotic therapy
- **Renal system**: candiduria, rising creatinine,

hypertension, flank mass, pyelonephritis, acute urinary obstruction from fungal mycetoma → hydronephrosis

- **CNS**: altered mental status, characteristic symptoms of meningitis
- **Optic**: chorioretinal infections, lens abscess
- **Hepatosplenic**: right upper quadrant pain; nausea, vomiting; hepatosplenomegaly
- **Other**: **endocarditis** (may be from central vascular catheters), bone/joint infections



Figure 84.3 Oral candidiasis on the tongue of a child who had recently taken oral antibiotics.

DIAGNOSIS

LAB RESULTS

- Microscopic examination
 - KOH preparation; visualization of hyphae, **pseudohyphae**, blastospores
- Invasive candidiasis
 - Blood/tissue culture
- PCR
- **Esophagitis**
 - Tissue biopsy (definitive)

OTHER DIAGNOSTICS

- Clinical presentation, history

TREATMENT**MEDICATIONS**

- Oropharyngeal candidiasis
 - Oral **nystatin** suspension; clotrimazole troches (dissolves in mouth)
- Candida dermatitis
 - Topical **nystatin**/miconazole
- Vulvovaginal candidiasis
 - Local miconazole/clotrimazole creams; oral **fluconazole**
- Invasive, systemic candidiasis
 - **Echinocandins**; voriconazole, caspofungin (preferred over amphotericin/fluconazole)
- Individuals with HIV
 - Prophylactic antifungals (e.g. oral nystatin, **fluconazole**)

OTHER INTERVENTIONS

- Candida dermatitis
 - Keep skin dry
- Invasive, systemic candidiasis
 - Immediate removal of all central lines, catheters (*Candida* can develop rapid biofilms)

CRYPTOCOCCUS NEOFORMANS

osms.it/cryptococcus-neoformans

PATHOLOGY & CAUSES

- **Heavily encapsulated**, nondimorphic, yeast-like fungus, urease positive
- Virulence factors
 - Grows well in 37°C/98.6°F environment
 - Produces polysaccharide capsule, melanin (neurotropism)
- Most common cause of fungal meningitis in immunocompromised adults
- Found in bird droppings, soil → inhalation of airborne fungi → evident/honevident pulmonary infection → **spreads lymphohematogenously** (can affect any organ) → **meninges**
- CNS infection associated with high mortality

RISK FACTORS

- Impaired cell-mediated immunity, high-dose corticosteroid treatment, hematologic malignancies (e.g. leukemia, lymphoma)
- HIV/AIDS (most common immunocompromising state): < 100 cells/mm³ CD4+ count

COMPLICATIONS

- Increased intracranial pressure → herniation → death
- May be due to buildup of cryptococcal polysaccharide at arachnoid villi → disruption in cerebrospinal fluid (CSF) reabsorption

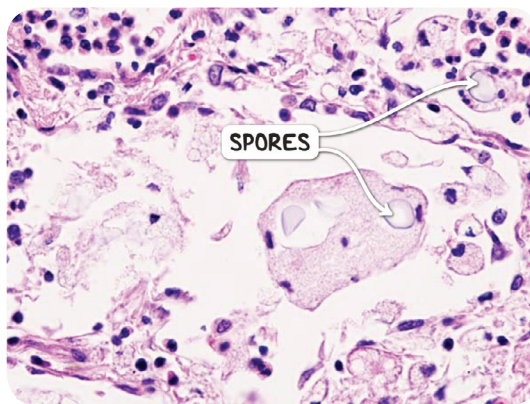


Figure 84.4 A histology photomicrograph of the lung.

SIGNS & SYMPTOMS

- Pulmonary manifestations
 - Asymptomatic in 1/3 of immunocompetent individuals; fever, cough, pleuritic chest pain, dyspnea, weight loss, hemoptysis
- Neurologic manifestations (most common)
 - Acute/insidious; headache, fever, vomiting, nuchal rigidity, mental status changes/seizures, cryptococcal abscesses (e.g. cryptococcomas, not common)
- Skin manifestations (10–15%)
 - Result of direct hematogenous spread/extension from bone lesion; single/multiple pustules/papules → ulcer/abscess
- Bone infection (5–10%)
 - Pain, swelling; joint involvement; often found incidentally

- Latex agglutination test
 - Detects polysaccharide capsular antigen, ↑ specificity

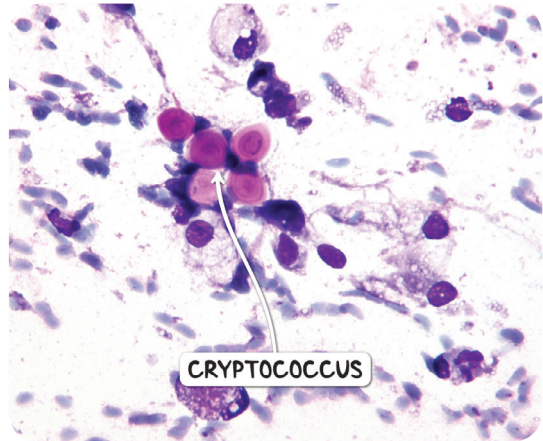


Figure 84.5 Bronchial washings from an immunocompromised individual with pulmonary cryptococcosis. The cryptococcus spores have a characteristically thick capsule.

DIAGNOSIS

DIAGNOSTIC IMAGING

Chest X-ray

- Focal/diffuse interstitial infiltrates, hilar lymphadenopathy

LAB RESULTS

- CSF
 - Lymphocytic pleocytosis; ↓ glucose; ↑ protein, opening pressure; results may be unchanged in individuals with AIDS
- Direct microscopic analysis of CSF/other body secretions
 - **India ink**: capsule visualized with clear halo
 - **Mucicarmine**: visualization of red inner capsule
 - Visualize budding
- Culture
 - **Sabouraud glucose agar**, incubation up to two weeks
- Cryptococcal capsular antigen (serum, CSF, urine, bronchoalveolar lavage)
 - Most reliable nonculture-based method

TREATMENT

MEDICATIONS

- Amphotericin B, flucytosine
- Prevention in HIV cases with CD4+ cell counts < 100 cells/mm³—fluconazole

OTHER INTERVENTIONS

- ↑ intracranial pressure complication treatment
 - Repeat CSF drainage (most important factor in reducing mortality)

MUCORMYCOSIS

osms.it/mucormycosis

PATHOLOGY & CAUSES

- Several genera of family Mucoraceae causing rapidly progressive, invasive mucormycosis in various body systems
- Subphylum Mucoromycotina, order Mucorales
 - Most human infections from members of family Mucoraceae
 - **Six genera:** *Rhizopus*, *Mucor*, *Actinomucor*, *Rhizomucor*, *Apophysomyces*
- Present in decomposing organic matter (e.g. spoiled food items, soil)
- Forms broad, aseptate hyphae branching at right angles by sexual reproduction with formation of zygospores
- **Inhalation of spores** → sinuses, lungs primary location of infection
- Immunocompetent host → lung macrophages ingest, kill spores → neutrophils kill hyphae
- Immunosuppressed individuals → macrophages fail to stop spore germination
- Severe neutropenia/diabetic ketoacidotic individuals → abnormal neutrophil function → increased risk of invasive infection
- Angioinvasive mold → results in thrombosis, infarction, necrosis of surrounding tissues
- Can affect all segments of GI tract (esp. stomach, small/large intestine, esophagus)
- Cutaneous mucormycosis
 - Due to traumatic implantation of spores from soil (e.g. site of surgical incisions, burn wounds)
 - Extensive necrotic infection → necrotizing cellulitis
 - Most common in immunocompetent individuals
- Disseminated mucormycosis (involves CNS)
 - Most common in severe neutropenic individuals following pulmonary infection
 - Brain (most commonly affected), metastatic necrotic lesions can occur in any organ

RISK FACTORS

- DM
- **Diabetic ketoacidosis state**
 - ↑ risk for rhinocerebral mucormycosis
- **Leukemia, neutropenia**, chemotherapy
 - ↑ risk of rhinocerebral, pulmonary, disseminated disease
- Severe malnutrition
 - GI mucormycosis
- Deferoxamine treatment for iron overload state
- Recipient of bone marrow transplant
- Prolonged use of corticosteroids/other immunosuppressive therapies
- Prolonged use of broad-spectrum antibiotics
- IV drug use

COMPLICATIONS

- **Cavernous sinus thrombosis**, cranial nerve palsies (e.g. proptosis, ptosis, dilation, fixation of pupil), vision loss,

Diseases

- **Rhinocerebral mucormycosis**
 - Necrotic lesion in paranasal sinus → orbit, face, palate, brain
 - Most common in diabetic ketoacidosis
 - Progresses rapidly
- Pulmonary mucormycosis
 - Most common in severe neutropenic individuals
- Gastrointestinal mucormycosis
 - Rare, occurs in severely malnourished children

brain abscess, necrosis of frontal lobes, GI tract perforation, perirenal abscess, renal infarction

SIGNS & SYMPTOMS

- **Typical course:** rapid onset of necrotic lesion → fulminant course requiring aggressive therapy
- **Rhinocerebral**
 - Black, necrotic lesion on nasal/palatine mucosa; nasal/sinus congestion, pain; epistaxis; fever; edema, induration, necrosis of perinasal, periorbital tissue
- **Pulmonary**
 - Nonspecific, pneumonia-like; may involve pleuritic chest pain, cough, fever, hemoptysis
- **GI**
 - Abdominal pain, bleeding (e.g. hematemesis)
- **Cutaneous**
 - Painful edema, erythema → raised, indurated lesions with black, necrotic center
- **Disseminated**
 - Altered mental status (e.g. lethargy, obtunded state, confused)

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan, MRI

- **Thoracic:** nodular lesions, cavitations
- **Head:** extension of infection in sinuses → affecting brain tissue

LAB RESULTS

- **Histopathological identification**
 - Distinct hyphae; broad irregularly branched with rare septations

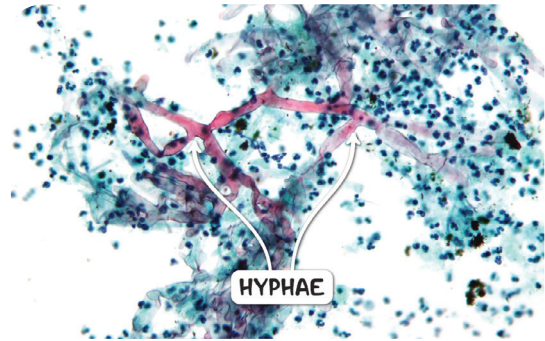


Figure 84.6 Bronchial washings stained with Papanicolaou stain from an individual with pulmonary mucormycosis. The mucor hyphae contain no septa, are of variable width and branch at a wide angle.

TREATMENT

MEDICATIONS

- Aggressive antifungal therapy
 - Amphotericin B

SURGERY

- Infected necrotic tissue
 - Extensive surgical debridement

OTHER INTERVENTIONS

- Adjunctive therapy
 - Hyperbaric oxygen, immune modulation, white blood cell infusion

PNEUMOCYSTIS JIROVECI (PNEUMOCYSTIS PNEUMONIA)

osms.it/pneumocystis-jirovecii

PATHOLOGY & CAUSES

- Opportunistic yeast-like fungi (originally classified as protozoan) responsible for pneumocystis pneumonia
- Formerly known as *Pneumocystis carinii*
- Airborne transmission route; human-to-human route occurs early in life
- Immunocompetent individuals may act as asymptomatic reservoirs
- 5–7 micrometer cysts contain up to eight pleomorphic intracystic sporozoites → become excysted → form trophozoites
- Reside in alveoli
- Disease: pneumocystis pneumonia
 - Occurs exclusively in immunocompromised individuals
 - Remains localized in lungs
 - Clinical manifestations due to inflammatory reaction in alveoli lumen/septum
 - Fatal if left untreated

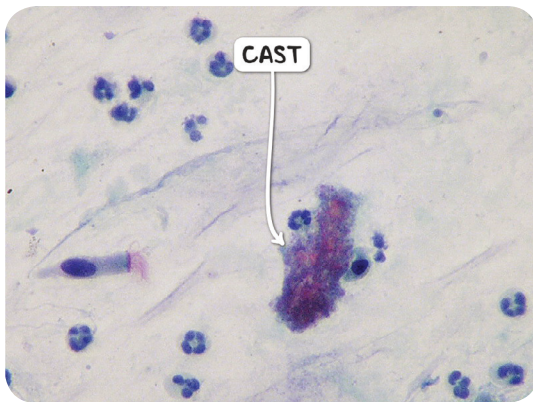


Figure 84.7 A foamy alveolar cast in a bronchial washing taken from an individual with *Pneumocystis pneumonia*.

RISK FACTORS

- Defects in cell-mediated immunity, HIV/AIDS, severe combined immunodeficiency syndrome, hematological malignancies, transplant recipients, hyper IgM syndrome

SIGNS & SYMPTOMS

- Most infections asymptomatic in immunocompetent individuals
- Abrupt onset of tachypnea, fever, cough
- Respiratory distress

DIAGNOSIS

DIAGNOSTIC IMAGING

Chest X-ray/CT scan

- Diffuse, bilateral ground glass opacities
- First appearing in perihilar area → progresses peripherally, apical regions spared

LAB RESULTS

- Microscopic examination with silver stain
 - Disc-shaped yeast
- Open lung biopsy
- Bronchoalveolar lavage
- PCR of sputum/lavage samples
- ↓ P_aO_2 (reflects severity of disease)
- Unchanged WBC count

TREATMENT

MEDICATIONS

- Trimethoprim-sulfamethoxazole
- Alternatives
 - Pentamidine, dapsone + trimethoprim, atovaquone

- Prophylactic trimethoprim-sulfamethoxazole/pentamide
 - Individuals with HIV, < 200 CD4+ cells/mm³

OTHER INTERVENTIONS

- Respiratory support

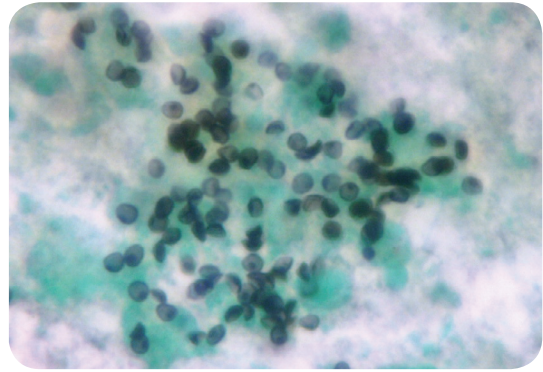


Figure 84.8 A bronchial wash stained with Grocott's methenamine silver highlighting *Pneumocystis* spores.

SPOROTHRIX SCHENCKII

osms.it/sporothrix-schenckii

PATHOLOGY & CAUSES

- Chronic subcutaneous thermally dimorphic fungus → **sporotrichosis**
- Found in soil, decomposing vegetation, plant materials (e.g. moss, hay, wood, rose bushes)
- Found worldwide, mostly in temperate/tropical regions (16–22°C/60.8–71.6°F)
- Outside human body grows as filamentous mold; **in tissue** grows as small **budding yeast** cells

Diseases

- Lymphocutaneous sporotrichosis
 - Follows **traumatic inoculation of skin/subcutaneous tissue** (e.g. minor insult from thorns or splinters) → incubation 1–4 weeks → papule develops at site of inoculation → **ulceration** of primary lesion → nonpurulent, odorless drainage → **similar lesions occur along lymphatic channel** proximal to primary lesion
- Pulmonary sporotrichosis
 - Following inhalation of *Sporothrix* conidia
 - May progress to disseminated disease

- Osteoarticular sporotrichosis
 - **Most commonly affected joints:** knee, elbow, wrist, ankle
 - Chronic infection with progressive decreased range of motion, pain, swelling
- Meningeal sporotrichosis
 - Rare, mostly in individuals with cellular immune defects (e.g. lymphoma, AIDS)
 - Chronic course
- Disseminated cutaneous sporotrichosis
 - Rare (< 1%)
 - Numerous small papules/vesicles → necrotic, ulcerated nodules on trunk, limbs
 - Follows lymphatic spread

RISK FACTORS

- Lymphocutaneous
 - Exposure due to skin trauma (e.g. living in homes with dirt floors)
 - Individual with outdoor preoccupation
 - Contact with cats
- Pulmonary
 - Chronic obstructive pulmonary disease (COPD)
- Excessive alcohol use

SIGNS & SYMPTOMS

- Lymphocutaneous sporotrichosis
 - Primary papule → ulcerated lesion; similar lesions visualized along lymphatic channel proximally; chronic, fixed cutaneous lesion
- Pulmonary
 - Fever, night sweats, weight loss, fatigue; dyspnea, cough; purulent sputum; hemoptysis
- Osteoarticular sporotrichosis; progressive decreased range of motion, pain, swelling in joints
- Meningeal sporotrichosis
 - Chronic (weeks to months) fever, headache



Figure 84.9 Partially healed skin lesions of sporotrichosis in a typical lymphocutaneous distribution.

DIAGNOSIS

DIAGNOSTIC IMAGING

Chest X-ray

- Unilateral/bilateral upper lobe cavities
- Variable amount of fibrosis
- Scattered nodular lesions

LAB RESULTS

- Culture (most sensitive)
 - Tissue biopsy, sputum, body fluid
 - Sabouraud's agar at room temperature
 - Characteristic arrangement of conidia on hyphae
- Direct microscopy
 - Typical oval/cigar-shaped cells
 - Asteroid bodies of *S. Schenckii*
- CSF analysis
 - Lymphocytic pleocytosis, ↑ protein, ↓ glucose

OTHER DIAGNOSTICS

- Clinical examination, history



Figure 84.10 Sporothrix fungi forming conidia.

TREATMENT

MEDICATIONS

- Localized: itraconazole
- Severe: amphotericin B